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CLINICAL ARTICLE

Obstetrics

Hematologic adaptation to mask-wearing among pregnant women and obstetrical outcome during the coronavirus disease 2019 pandemic

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Abstract

Objective: To evaluate the effect of the coronavirus disease 2019 (COVID-19) mask-wearing on hematological laboratory components and obstetrical outcomes among women delivering during the COVID-19 pandemic.

Methods: Laboratory results and obstetrical outcomes of women with singleton gestations, admitted for delivery during the COVID-19 mask-wearing period (April–June 2020) were compared with those of women delivering during the parallel period in 2019 and with a larger cohort derived from nine pre-pandemic years (March 2011–April 2020).

Results: Overall, 1838 women delivered during the COVID-19 pandemic. Compared with the pre-pandemic period, mean hemoglobin and fibrinogen levels were significantly higher during the mask-wearing period (12.15 ± 1.1 vs 11.96 ± 1.2, $P < 0.001$ and 472 ± 103.6 vs 448 ± 85.1 mg/dl, $P < 0.001$, respectively). Platelet levels were lower (200 ± 56.0 vs 206 ± 57.5 K/μl, $P < 0.001$). The rate of delivery at <34 weeks of gestation was lower during the mask-wearing period (1.1% vs 2%, odds ratio [OR] 0.57, 95% confidence intervals [CI] 0.37–0.88, $P = 0.01$), whereas cesarean delivery and postpartum hemorrhage rates were higher (26.7% vs 24.4%, OR 1.13, 95% CI 1.02–1.25, $P = 0.022$ and 4.1% vs 2.8%, OR 1.5, 95% CI 1.2–1.8, $P = 0.001$, respectively).

Conclusion: A hard-to-ventilate space created by wearing a mask during the COVID-19 era may be the underlying cause of the observed higher hemoglobin level among pregnant women, possibly affecting obstetrical outcomes.

KEYWORDS
cesarean delivery, coronavirus disease 2019, hemoglobin, mask-wearing, preterm birth

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, China, and resulted in an ongoing pandemic. On March 19, 2020, the Israeli government declared a national state of emergency. Starting on April 12, 2020, the Israeli population, including pregnant women, were obligated to wear a face mask whenever outside the home. Mask-wearing over the mouth and nose creates a hard-to-ventilate space, a micro-environment consisting of low oxygen (O_2) and high carbon dioxide (CO_2) concentrations,[1]

that may lead to respiratory acidosis and elevated hemoglobin.[2] In addition, mask-wearing may induce relative hypoxia,[1,3] stimulating erythropoietin secretion, leading to red blood cell production in the bone marrow and therefore elevated hemoglobin levels.[4]

Currently, governments are formulating regulations to suppress the spread of COVID-19, and a better understanding of the consequences of these regulations is required. The hematological impact of wearing a mask during the COVID-19 era is understudied. This study aimed to underline the association of low O_2 and high CO_2 concentrations inhaled when wearing a mask and parturient hematologic and obstetrical outcomes.

2 | MATERIALS AND METHODS

This was a retrospective cohort study conducted at a single university-affiliated, tertiary medical center. The center treats a heterogeneous population with over 10 000 deliveries per year. The study cohort included pregnant women admitted to the obstetrical emergency unit for delivery during the mask-wearing period of the COVID-19 pandemic (April 19–June 27, 2020), starting 7 days after initiation of the mask-wearing regulations in Israel, to account for the delay between erythropoietin secretion and the rise in hemoglobin levels. We compared these women's characteristics and outcomes to two pre-pandemic time frames: the parallel period in 2019 (April 19–June 27, 2019) and a more extended period between March 21, 2011 and April 18, 2020.

We abstracted labor and delivery charts from the electronic medical record database of the labor and delivery ward of our center. The following data were evaluated: patient characteristics (age, body mass index, smoking, COVID-19 infection status and hemoglobin, platelets, fibrinogen, and white blood cell levels); delivery and postpartum characteristics (pregnancy duration at delivery, mode of delivery, postpartum hemorrhage, blood product transfusion); neonatal outcomes including birth weight, Apgar score, umbilical artery pH and base excess, neonatal intensive care unit (NICU) admission, stillbirth, neonatal death, mechanical ventilation, hypoxic ischemic encephalopathy, convulsions, asphyxia, and hypothermic treatment.

Maternal body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) was calculated according to height and weight at admission. Postpartum hemorrhage was defined by the American College of Obstetricians and Gynecologists as cumulative blood loss of 1000 ml or more, or as blood loss accompanied by signs or symptoms of hypovolemia within 24 h of the birth process. Composite bleeding was defined as the presence of postpartum hemorrhage or blood products transfusion. The composite neonatal outcome included the presence of any of the neonatal outcomes studied.

Patient characteristics are described as proportions for categorical variables and as means and standard deviations for continuous variables. Significance between study groups was assessed by χ^2 test and Fisher's exact test for categorical variables, *t* test and Mann–Whitney *U* test were used as appropriate in relation to cohort distribution. We further divided the whole study cohort into two groups: hemoglobin <11 and 11 g/dl or more. A logistic regression analysis was performed to underline independent determinants associated with hemoglobin levels below 11 g/dl. The model included variables with a potential association with hemoglobin level, age, BMI, smoking status, parity, gestation at delivery, and the period evaluated with respect to the COVID-19 pandemic. A two-sided *P* value <0.05 indicated statistical significance. The data were analyzed using SPSS version 24 (IBM Corp., Armonk, NY, USA).

This article does not contain any studies with human participants or animals performed by any of the authors. Ethical approval was waived by the local ethics committee of Sheba Medical Center in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Institutional review board approval was obtained for this retrospective study on March 30, 2020 (# 7068-20-SMC).

3 | RESULTS

From April 19 to June 27, 2020, 1838 women were referred to the delivery unit, compared with 88 973 women between March 21, 2011 and April 18, 2020. A comparison of clinical parameters, delivery data, and neonatal outcomes between the mask-wearing period and pre-pandemic periods is presented in Table 1. Compared with the 2011–2020 pre-pandemic period, the mean hemoglobin levels and the proportion of women with hemoglobin above 13 g/dl were significantly higher during the mask-wearing period (12.15 ± 1.1 vs 11.96 ± 1.2 g/dl, *P* < 0.001; 21.5% vs 16%, OR 1.43, 95% CI 1.28–1.61, *P* < 0.001, respectively), whereas the proportion of women with hemoglobin below 11 g/dl was lower (13.5% vs 16.5%, OR 0.79, 95% CI 0.69–0.91, *P* = 0.01). Platelet levels were lower during the pandemic period compared with the pre-pandemic period (200 ± 56.0 vs 206 ± 57.5 K/μl, *P* < 0.001), whereas fibrinogen levels were higher (472 ± 103.6 vs 448 ± 85.1 mg/dl, *P* < 0.001). Cesarean delivery rates were higher during the mask-wearing period compared with the pre-pandemic period (26.7% vs 24.4%, OR 1.13, 95% CI 1.02–1.25, *P* = 0.022), but rates of delivery before 34 weeks of pregnancy were lower (1.1% vs 2%, OR 0.57, 95% CI 0.37–0.88, *P* = 0.010). The rate of postpartum hemorrhage and the composite bleeding rate were higher during the mask-wearing period (4.1% vs 2.8%, OR 1.5, 95% CI 1.2–1.8, *P* = 0.01 and 5.1% vs 3.8%, OR 1.3, 95% CI 1.07–1.60, *P* = 0.07, respectively).

A comparison between the mask-wearing period and the parallel period in 2019 demonstrated the same hematologic findings, rates of preterm delivery before 34 weeks of pregnancy, and postpartum hemorrhage.

Neonatal outcomes are presented in Table 2. Mean birth weights were higher during the mask-wearing period compared with the 2011–2020 pre-pandemic period (3232 vs 3200 g, *P* = 0.009). Incidence of neonatal Apgar score <5 at 1 min after delivery was lower during the mask-wearing period, as were NICU admissions (0.2% vs 0.6%, OR 0.36, 95% CI 0.13–0.97, *P* = 0.03; 2.8% vs 3.7%,

TABLE 1 Comparison of clinical parameters, delivery data and neonatal outcomes between the mask-wearing period and pre-pandemic periods[a]

Characteristic	Mask-wearing period (April–June 2020) (*n* = 1838)	Pre-pandemic period (March 2011–April 2020) (*n* = 88 973)	OR (95% CI)	*P* value	Pre-pandemic period (April–June 2019) (*n* = 1890)	OR (95% CI)[b]	*P* value
Background and laboratory characteristics							
Age, year	32 ± 5.3	32 ± 5.21	—	0.165	32 ± 5.3	—	0.944
BMI	28.3 ± 4.5	28.1 ± 4.4	—	0.057	28.4 ± 4.6	—	0.458
Smoking	84 (4.6%)	4111 (4.6%)	—	0.919	72 (3.8%)	—	0.245
COVID-19 positive	6	4[b]	—		4[c]	—	
Parity	1± 1.4	1 ± 1.4	—	0.139	1 ± 1.63	—	0.286
Hb, g/dl	12.15 ± 1.1	11.96 ± 1.2	—	<0.001	12.00 ± 1.1	—	<0.001
Hb >13.0	395 (21.5%)	14 244 (16.0%)	1.43 (1.28–1.61)	<0.001	338 (17.9%)	1.26 (1.07–1.49)	0.005
Hb >14.0	61 (3.3%)	2202 (2.5%)	1.35 (1.04–1.75)	0.022	58 (3.1%)	–	0.662
Hb <11	249 (13.5%)	14 638 (16.5%)	0.79 (0.69–0.91)	0.001	303 (16.0%)	0.82 (0.68–0.98)	0.033
PLT, K/µl	200 ± 56.0	206 ± 57.5	—	<0.001	210 ± 58.8	–	<0.001
PLT <150 K/µl	302 (16.4%)	11 928 (13.4%)	1.27 (1.12–1.43)	<0.001	203 (10.7%)	1.63 (1.35–2.0)	<0.001
WBC, K/µl	10.87 ± 2.9	11.40 ± 3.2	–	<0.001	10.99 ± 3.2	–	0.341
Fibrinogen, mg/dl	472 ± 103.6	448 ± 85.1	–	<0.001	468 ± 95.0	–	0.590
Fibrinogen >500 mg/dl	195 (10.6%)	4465 (5.0%)	2.24 (1.93–2.61)	<0.001	172 (9.1%)	–	0.121
Fibrinogen >600 mg/dl	62 (3.4%)	1276 (1.4%)	2.39 (1.85–3.11)	<0.001	40 (2.1%)	1.63 (1.08–2.43)	0.019
Delivery characteristics							
Gestation at delivery, weeks	$39^{1/7} \pm 1^{5/7}$	$39^{1/7} \pm 2^{0/7}$	—	0.693	$39^{0/7} \pm 2^{2/7}$	—	0.058
<$37^{0/7}$ weeks	130 (7.1%)	6398 (7.2%)	—	0.846	154 (8.1%)	—	0.195
<$34^{0/7}$ weeks	21 (1.1%)	1765 (2.0%)	0.57 (0.37–0.88)	0.010	56 (3.0%)	0.37 (0.23–0.62)	<0.001
<$32^{0/7}$ weeks	13 (0.7%)	1150 (1.3%)	0.54 (0.31–0.94)	0.027	35 (1.9%)	0.37 (0.19–0.72)	0.002
Spontaneous delivery	1220 (66.4%)	61 786 (69.4%)	0.86 (0.78–0.95)	0.005	1,239 (65.6%)	—	0.606
OVD	127 (6.9%)	5487 (6.2%)	—	0.191	137 (7.2%)	—	0.690
Cesarean delivery	491 (26.7%)	21 700 (24.4%)	1.13 (1.02–1.25)	0.022	514 (27.2%)	—	0.720
Intrapartum CD	131 (26.7%)	5488 (25.3%)	—	0.480	143 (27.8%)	—	0.695
Postpartum hemorrhage	76 (4.1%)	2470 (2.8%)	1.5 (1.20–1.80)	0.001	53 (2.8%)	1.49 (1.04–2.13)	0.026
Blood products transfusion	33 (1.8%)	1489 (1.7%)	—	0.780	35 (1.9%)	—	0.898
Composite bleeding[d]	93 (5.1%)	3347 (3.8%)	1.3 (1.07–1.60)	0.007	78 (4.1%)	—	0.173

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CD, cesarean delivery; CI, confidence interval; COVID-19, coronavirus disease 2019; Hb, hemoglobin; OR, odds ratio (calculated only for significantly different categorical variables); OVD, operative vaginal delivery; PLT, platelets; WBC, white blood cells.

[a]Values are presented as mean ± standard deviation or number (percentage).

[b]Compared with the mask-wearing period.

[c]COVID-19 infection was evaluated only during the COVID-19 pandemic.

[d]Composite bleeding was defined as the presence of postpartum hemorrhage of blood products transfusion.

TABLE 2 Comparison of neonatal outcomes between the mask-wearing period and pre-pandemic periods[a]

Characteristic	Mask-wearing period (April–June 2020), (*n* = 1838)	Pre-pandemic period (March 2011–April 2020), (*n* = 88 973)	OR (95% CI)	*P* value	Pre-pandemic period (April–June 2019), (*n* = 1890)	OR (95% CI)[b]	*P* value
Birth weight	3232 ± 513	3200 ± 533	—	0.009	3190 ± 552	—	0.015
Apgar 1 min	9 ± 0.9	9 ± 1.1	—	0.038	9 ± 1.0	—	0.708
Apgar 5 min	10 ± 0.9	10 ± 1.1	—	0.132	10 ± 1.0	—	0.711
Apgar 1 min <5	4 (0.2%)	532 (0.6%)	0.36 (0.13–0.97)	0.030	8 (0.4%)	—	0.388
Apgar 5 min <7	6 (0.3%)	306 (0.3%)	—	0.899	5 (0.3%)	—	0.727
Umbilical artery pH <7.0	1 (0.1%)	170 (0.2%)	—	0.181	9 (0.5%)	0.11 (0.01–0.90)	0.021
Umbilical artery base excess >12	8 (0.4%)	362 (0.4%)	—	0.852	9 (0.5%)	—	0.854
NICU admission	51 (2.8%)	3253 (3.7%)	0.75 (0.56–0.99)	0.046	95 (5.0%)	0.54 (0.38–0.76)	<0.001
Stillbirth	14 (1.5%)	911 (1.0%)	—	0.268	15 (0.8%)	—	0.913
Death in 24 h	1 (0.1%)	43 (0.01%)	—	0.593	1 (0.1%)	—	1.0
Death in 30 d	3 (0.2%)	79 (0.1%)	—	0.231	3 (0.2%)	—	1.0
Mechanical ventilation	16 (0.9%)	812 (0.9%)	—	0.851	17 (0.9%)	—	0.926
Hypoxic ischemic encephalopathy	1 (0.1%)	86 (0.1%)	—	1.0	2 (0.1%)	—	1.0
Convulsions	1 (0.1%)	101 (0.1%)	—	0.727	4 (0.2%)	—	0.375
Asphyxia	0 (0%)	73 (0.1%)	—	0.409	1 (0.1%)	—	1.0
Cooling protocol	1 (0.1%)	68 (0.1%)	—	1.0	2 (0.1%)	—	1.0
Composite neonatal outcome[c]	70 (3.8%)	4184 (4.7%)	—	0.073	110 (5.8%)	0.64 (0.47–0.87)	0.004

Abbreviations: CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio (calculated only for significantly different categorical variables).

[a]Values are presented as mean ± standard deviation or number (percentage).

[b]Compared with the mask-wearing period.

[c]Composite neonatal outcome comprising any of the following: stillbirth, neonatal death during the first 24 h, mechanical ventilation during the first 24 h, asphyxia, hypoxic ischemic encephalopathy, and neonatal intensive care unit admission.

OR 0.75, 95% CI 0.56–0.99, $P = 0.046$, respectively). Compared with the parallel period in 2019, the composite neonatal outcome rate was lower during the mask-wearing period (3.8% vs 5.8%, OR 0.64, 95% CI 0.47–0.87, $P = 0.004$). The same trend of higher birth weight and NICU admission during the mask-wearing period compared with the parallel period in 2019 was observed ($P = 0.015$ and $P < 0.001$, respectively).

Further dividing the whole study cohort into two groups; a group with hemoglobin less than 11 g/dl and the other with hemoglobin of 11 g/dl or more, we performed a multivariate regression analysis, which identified that the pre-pandemic period was independently associated with hemoglobin level below 11.0 g/dl (Table 3).

4 | DISCUSSION

This comparative study of the current COVID-19 pandemic versus the pre-pandemic period reported an increase in hemoglobin and fibrinogen levels and a decrease in platelets and white blood cell levels. The periods analyzed were independently associated with hemoglobin level after adjusting for confounders in a regression analysis. Additionally, we report an increase in postpartum hemorrhage and a decrease in preterm delivery, before 34 weeks of pregnancy, and in the occurrence of composite neonatal outcome during the mask-wearing period.

The impact of airflow-restricting-masks was previously shown to facilitate hemoglobin production.[2,5] Accordingly, we demonstrated increased hemoglobin levels during the COVID-19 pandemic, during which wearing of masks covering the mouth and nose was obligatory. Elevated hemoglobin levels can protect against anemia during pregnancy, which has been associated with adverse obstetrical outcomes, including preterm birth.[6,7] The decrease in preterm birth at <34 weeks of gestation found in our study may result from the mildly elevated hemoglobin levels during the pandemic period. However, preterm birth rates during the COVID-19 pandemic are still disputed.[8,9] During the pandemic period, during which the population was instructed to wear a face mask, we found increased fibrinogen levels and decreased platelet levels. These findings match the results of studies conducted to examine the impact of long-term hypoxic exposure.[10] Mild platelet decrease was previously associated with higher postpartum hemorrhage rates,[11] which corresponds with the present study's results.[11]

Wearing face masks plays a substantial role in preventing the spread of COVID-19.[12] However, using face masks that restrict airflow was previously described as being associated with elevated hemoglobin levels.[2,5] The micro-environment present within the mask's hard-to-ventilate space, consisting of low O_2 and high CO_2 concentrations, may result in decreased oxygen saturation (Sao_2)[3] and elevation in the partial pressure of carbon dioxide (Pco_2),[13] respectively. The relative hypoxia induced by a low inhaled O_2 concentration may stimulate erythropoietin secretion, which in turn increases reticulocyte production, which eventually mature into red blood cells.[14] A previous study by Vij[10] investigated the effect of chronic hypoxia on hematologic parameters. The study followed hemoglobin, fibrinogen, platelets, and white blood cell concentrations of 40 healthy men at sea level and at the following 3- and 13-month sojourns at high altitude. The study's results suggest that a prolonged stay at high altitude leads to elevated hemoglobin and fibrinogen levels and lower platelet and white blood cell levels.[10]

It is also possible that hemoglobin, which has a role as a Pco_2 buffer to prevent acidosis, may arise secondary to acidosis induced by mask-wearing.[2]

It should be noted that the studies mentioned above evaluated the effect of face-mask-wearing on blood hemoglobin levels using different mask types, and neither the duration of mask-wearing nor the physical activity measured was accounted for. Furthermore, it is important to acknowledge that there is no consensus regarding the hypoxemic effect of mask-wearing, as different studies among different populations with various methodological approaches have been used,[15] reaching conflicting results.

There is a debate regarding the impact of hypoxia on other, non-hemoglobin, hematologic parameters. However, when examining long-term hypoxia exposure, previous research has found elevated fibrinogen levels and lower platelet levels, in accordance with our results.[10]

As for the clinical aspects of the data collected in our study, we have found higher postpartum hemorrhage rates during the mask-wearing period and a lower platelet count. The American College of Obstetricians and Gynecologists classifies platelet count less than 70 K/μl as a risk factor for postpartum hemorrhage. Nevertheless, it was previously reported that there is a two-fold greater likelihood of postpartum hemorrhage among women with mild thrombocytopenia (platelet count 100–149 K/μl).[11] Our results may reflect the same consequences of mild thrombocytopenia on postpartum hemorrhage rates.

The elevated hemoglobin levels may be a plausible explanation for our reported lower rates of preterm birth and composite neonatal outcome. Hemoglobin concentrations greater than 14.6 g/dl at prenatal visits were previously associated with an increased risk of preterm birth, stillbirth, and growth restriction.[16,17] Conversely, relative elevations of hemoglobin levels can protect against anemia

TABLE 3 Multivariate analysis of factors associated with hemoglobin <11 g/dl

Variable	aOR (95% CI)	*P* value
Pre-pandemic period	1.39 (1.22–1.58)	<0.001
Age, year	1.02 (1.22–1.58)	<0.001
BMI	1.001 (0.998–1.005)	0.475
Smoking	0.70 (1.12–1.48)	<0.001
Parity	0.78 (0.77–0.79)	<0.001
Pregnancy duration	1.09 (1.08–1.10)	<0.001

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval.

during pregnancy, which has been previously associated with adverse obstetrical outcomes, including preterm birth, low birth weight, stillbirth, and neonatal mortality.[6,7] These results can potentially reflect the effect of anemia correction due to hemoglobin elevation. Additionally, a proposed underlying mechanism for the pregnancy outcomes is the induction of heme oxygenase-1 during hypoxia.[18] Heme oxygenase-1 induction has been shown to improve pregnancy outcomes, and to reduce the rate of placenta-mediated complications[19] and spontaneous preterm birth.[20]

Reports of preterm birth rates during the COVID-19 pandemic are scarce and mainly include women infected with COVID-19.[21,22] A previous report regarding preterm births during the pandemic among women who were mostly not infected with COVID-19 did not find a difference in preterm birth rates.[23] A possible explanation for the difference between the two studies is the different populations studied and different sample sizes.

Masks restricting the airflow may reduce ventilation and respiratory rate.[24] Alongside spirometric alterations, masks may lead to hematologic changes such as increased hemoglobin levels, CO_2 accumulation, and decreased oxygen saturation, as described above. It is possible that populations suffering from impaired pulmonary or cardiac function, such as those with chronic obstructive pulmonary disease, heart failure, or asthma, may bear increased sensitivity to factors overloading these systems.[25,26]

The retrospective design of this study raises the possibility of the biases inherent to such investigations. As a result, we cannot exclude the possibility that additional unknown factors could explain the differences observed between the groups.

Moreover, although some women wear a surgical mask, others prefer to wear an N-95 mask, a variation not accounted for by our study. Additionally, although significant, we underline small hematologic variations observed between study groups, of which the clinical impact should be further studied. Nonetheless, these mild differences may have been disguised by patients who spent shorter time periods wearing a mask throughout the day, or by the short period of time evaluated after wearing a mask became obligatory.

Additionally, we did not analyze blood gases and Sao_2, so we can only rely on the blood count data to determine whether patients were hypoxic or hypercapnic.

Finally, the conduct of the study in a single tertiary care center may limit the generalizability of the results. On the other hand, the main strengths of our study include its relatively large cohort of patients and the meticulous data collection on a broad set of variables.

The present study demonstrates significant hematologic changes among pregnant women admitted to the obstetrical emergency unit during the COVID-19 pandemic after the initiation of mask-wearing regulations. Our clinical results present a decrease in composite neonatal outcomes and lower preterm birth rates, possibly secondary to elevated hemoglobin levels measured during the COVID-19 pandemic. These hematologic changes may have a substantial impact on high-risk non-pregnant populations as well. Further research is required to better understand the consequences of long-term mask-wearing among high-risk populations, including pregnant women.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

LF, NM, GL, YY, and RM contributed to the conception and design of the work. LF, GL, YB, AT, and RM contributed to the acquisition and interpretation of the data. LF, GL, and RM wrote the paper. All authors revised and approved the final manuscript.

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